PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001654	15.04.2004	15.04.2003

International Patent Classification (IPC) or both national classification and IPC
A61K51/04, A61P35/00

Applicant
ALGETA AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001654

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	15-20
	No:	Claims	1-14 (cf. separate sheet)

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 2004/043487 A (BRACCO IMAGING SPA ; DE HAEEN CHRISTOPH (IT)) 27 May 2004 (2004-05-27)

D2: US 2001/008625 A1 (LARSEN ROY H ET AL) 19 July 2001 (2001-07-19)

D3: WO 01/60417 A (LARSEN ROY H ; ANTICANCER THERAPEUTIC INV S A (NO); HENRIKSEN GJERMUND) 23 August 2001 (2001-08-23)

D4: MILENIC D E ET AL: "In vivo comparison of macrocyclic and acyclic ligands for radiolabeling of monoclonal antibodies with <177>Lu for radioimmunotherapeutic applications" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 29, no. 4, May 2002 (2002-05), pages 431-442, XP004357346 ISSN: 0969-8051

D5: WO 01/66155 A (FRANK R KEITH ; SIMON JAIME (US); GULYAS GYONGYI (US); KIEFER GARRY E) 13 September 2001 (2001-09-13)

D6: WO 02/05859 A (COCKBAIN JULIAN ; LARSEN ROY H (NO); ANTICANCER THERAPEUTIC INV S A (N) 24 January 2002 (2002-01-24)

Novelty - Article 33(2) PCT

D2 (US2001008625) discloses receptor conjugates with an antibody and a radionuclide such as ^{227}Th (cf. claims 1-4) to be used in the treatment of different soft-tissue cancer forms (cf. claim 20). Kits where the radioligand and the antibody are separate are also described (cf. claims 22, 23).

D3 (WO 01/60417) discloses conjugate systems comprising a liposome with a chelator, such as DOTA (cf. claim 3) and a heavy alpha-emitter such as ^{227}Th (cf. claim 12). The liposomes may be conjugated to antibodies and are useful in the treatment of various non-skeletal cancer forms (cf claim 30). Kits where the liposomes, the radionuclide and the targeting molecule are in separate vials are disclosed (cf. claims 31, 32).

The disclosure of D2 and D3 appears to destroy novelty for the subject-matter of the independent claims 1, 15, 16, 19 and 20.

Inventive Step - Article 33(3) PCT

An inventive step can only be assessed when novelty has been established for the independent claims.

Industrial Applicability - Article 33(4) PCT

For the assessment of the present claims 1-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/421,244	04/23/2003	Roy H. Larsen	50147/006001	4638

21559 7590 01/12/2007

CLARK & ELBING LLP
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BOSTON, MA 02110

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/421,244	LARSEN ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,7 and 9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4,6,7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "**said**," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

2. Claims 7 and 9 are objected to because of the following informalities: The claim language for the Markush groups of the instant claims 7 and 9 is not in the proper form. Markush group claim terminology should read as follows “selected from the group consisting of..”. Appropriate correction is required.

3. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 6 recites “ acceptably non-myelotoxic quantity is less than 150kBq of radium-223 per kilogram bodyweight” which is broader than the “acceptably non-myelotoxic quantity of radium-

223 of at least 40kBq/kg" of the claim 1 to which it depends. Therefore the instant claim 6 is not further limiting of the independent claim 1 to which it depends.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Larsen et al. (WO02/05859A2).

6. Larsen et al. (WO02/05859A2) teaches of the method of treating a malignant soft-tissue disease (p1, lines 1-12; p9, lines 24-31) by administering to a mammalian subject (p9, lines 6-7) a ^{227}Th-chelator complex, not excluding non-liposomal radiopharmaceutical complexes (p4, line 35; p7, lines 19-24). The decay of the ^{227}Th generates in vivo an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area (p6, lines 33-37; p11, line 12) where ^{223}Ra is the first daughter nuclide in the emissions cascade of ^{227}Th. The preparation of the ^{227}Th-chelator complex for administration may be in a pharmacologically acceptable carrier (p8, line 37). It is clearly disclosed that the ^{227}Th-chelator complex is also targeted to bone as well as bone surfaces where soft tissue, such as bone marrow is located. The ^{227}Th-chelator complex is used to irradiate the bone surface with α-particles to inactivate microscopic deposits of cancer cells on the bone surfaces (p7,

lines 33-36). It is disclosed that that the complex be preferentially distributed to the bone but it is also disclosed that the ratio of distribution of the complex to femur to liver (soft tissue) is from 3:1, 8:1 or at best 15:1, etc. (p4, lines 3-15; p15, lines 20-35). Therefore the disclosure anticipates that the 227Th-chelator complex will be targeted to soft-tissue as the authors state that they anticipate at least some soft-tissue targeting. The instant claims do not provide for any structural limitations to differentiate the radionuclide complex of the disclosure which is within the scope of soft tissue targeting radionuclide complex and also due the proximity of the bone and soft tissue, such as bone marrow. The dosages of the ^{227}Th-chelator complex of the disclosure encompass those of the instant claims and are taught to reduce myelotoxicity and therefore they would generate the acceptably non-myelotoxic quantity of the daughter radionuclide ^{223}Ra. Therefore the administration of such doses would also cause reduction of the neutrophil cell count to a nadir no less than 10% of the count prior to treatment.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1,2,4,6,7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (WO02/05859A2) in view of .

9. Larsen et al. (WO02/05859A2) discloses the method of treating a malignant soft-tissue disease (p1, lines 1-12; p9, lines 24-31) by administering to a mammalian subject (p9, lines 6-7) a ^{227}Th-chelator complex, not excluding non-liposomal radiopharmaceutical complexes as well as that listed above. Also, the method of treating a soft tissue disease includes those diseases such as cancer (i.e. myeloma, etc.) (p9, lines 24-35) and includes reducing myelotoxicity (p8, line3). The kits for the preparation of the ^{227}Th-chelator complex used for the treatment of malignant soft tissue disease include the ^{227}Th radioisotope, the radioisotope chelate and for the preparation of a solution, the pharmaceutically acceptable carrier (p10, lines 18-32). The dosage administered to a patient of the ^{227}Th-chelator complex varies between approximately 10kBq-2MBq/kg bodyweight (p10, lines 14-15). This dosage range encompasses that of the instant claims, such as 75kBq/kg and 36-200kBq/kg. Furthermore, it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

10. Inverardi et al. (US 2003/0228256A1) discloses the administration of a bone seeking radionuclide-ligand complex where the radionuclide may be ^{223}Ra and the ligand is an aminophosphonic acid (p3, [0033]). The radionuclide-ligand complexes can be administered to a patient in pharmaceutically acceptable dosage forms and can be

localized into bone and other tissues (p4, [0036] and [0038]). The radioactivity will remain in recipient bone thereby affecting the bone marrow or bone marrow-derived cells therein, for the life of the isotope (p4, [0037]). The patient may also be administered stem cells (p4, [0038]).

11. Goldenberg (US 6,083,477) discloses a toxin-ligand conjugate that binds to a specific cellular surface marker on a cell and its method of use for tumor therapy (column 1, lines 11-16). It is disclosed that doses of antibody and or radioactivity usually require stem cell rescue and the goal for such is to decrease myelotoxicity generated by an antibody-radionuclide composition (column 1, lines 40-47). The conjugate of the disclosure is a toxin-therapeutic radionuclide-IL-15 complex where IL-15 is a fusion protein comprising a bispecific antibody that has a specificity for a cell marker specific to a malignant cell thereby localizing the toxin-therapeutic radionuclide-IL-15 complex effectively to a desired cancer site (column 2, lines 34-38). This complex is useful for the treatment of leukemias and lymphomas (column 2, lines 40-42).

12. At the time of the invention it would have been obvious to one ordinarily skilled in the art to employ the step of stem cell therapy of as disclosed by Inverardi et al. (US 2003/0228256A1) or Goldenberg (US 6,083,477) since it is known in the art to be used in conjunction with radiotherapy. The ^{223}Ra-ligand complexes as seen by Inverardi et al. could localized into bone and other tissues as does the ^{227}Th-chelator complex of Larsen et al. (WO02/05859A2) and the radioactivity will remain affect the bone marrow or bone marrow-derived cells therein, for the life of the isotope. Therefore it would be obvious that the daughter radionuclide of the ^{227}Th-chelator complex would be

generated and at least partially localized into the soft tissue as Larsen et al. describes. The decay of the ^{227}Th generates an emissions cascade of α-particles, such as the daughter radionuclide ^{223}Ra that will occur in the target area where ^{223}Ra is the first daughter nuclide in the emissions cascade of ^{227}Th. The dose of 223-Ra is dependent on the decay properties of ^{227}Th radionuclide and since the dosage of Larsen et al. encompasses that of the instant claims, the dose of ^{223}Ra generated in vivo would be equivalent also obviously encompass that of the instant claims.

It is respectfully pointed out that instant claim 15 is a product-by-process limitation. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1,2,4,6,7 and 9-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10,18 and 19 of copending Application No. 10/552,876. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the copending application 10/552,876 are both drawn to the method for treating malignant soft tissue disease in a mammalian subject via administration of a thorium-227 conjugate comprising an antibody. Also the generation of radium-223 via administration of a thorium-227 conjugate of the copending application 10/552,876 encompasses the generation of 40kBq/kg or less than 150kBq/kg of radium-223 via administration of 36-200kBq/kg or more specifically 75kBq/kg of the thorium-227 conjugate of the instant claims. The diseases to be treated by the thorium-227 conjugate include carcinomas, sarcomas, myelomas, etc. The subjects of the instant claims and of the copending application 10/552,876 are treated with stem cells to combat the myelotoxicity of the radium-223 generated. The kits of the instant claims are encompassed by those of the copending application 10/552,876.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
January 4, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER